PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference P-0410	**FOR FURTHER ACTION**	See Form PCT/IPEA/416
International application No. PCT/HU2004/000043	International filing date *(day/month/year)* 27.04.2004	Priority date *(day/month/year)* 28.04.2003
International Patent Classification (IPC) or national classification and IPC C07D403/04, C07D403/10, C07D401/04, C07D403/12, C07D495/04, C07D401/12		
Applicant HIDEG, Kalman et al.		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 8 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☒ *sent to the applicant and to the International Bureau)* a total of 12 sheets, as follows:
      ☐ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☒ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the opinion
☐	Box No. II	Priority
☒	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☒	Box No. VIII	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
28.02.2005	02.09.2005
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Kirsch, C Telephone No. +49 89 2399-2191

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/HU2004/000043

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:

   ☐ international search (under Rules 12.3 and 23.1(b))
   ☐ publication of the international application (under Rule 12.4)
   ☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

Description, Pages	
2-26	as originally filed
1	filed with telefax on 02.03.2005
Claims, Numbers	
1-21	filed with telefax on 28.02.2005
Drawings, Sheets	
1/5-5/5	as originally filed
6/7, 7/7	filed with telefax on 02.03.2005

☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:

   ☐ the description, pages
   ☐ the claims, Nos.
   ☐ the drawings, sheets/figs
   ☐ the sequence listing *(specify)*:
   ☐ any table(s) related to sequence listing *(specify)*:

4. ☒ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).

   ☒ the description, pages 1
   ☒ the claims, Nos. 1-10, 12-21
   ☒ the drawings, sheets/figs 6/7-7/7
   ☐ the sequence listing *(specify)*:
   ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/HU2004/000043

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 20

because:

☒ the said international application, or the said claims Nos. 20 relate to the following subject matter which does not require an international preliminary examination (specify):

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos.

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form
- ☐ has not been furnished
- ☐ does not comply with the standard

the computer readable form
- ☐ has not been furnished
- ☐ does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☒ See separate sheet for further details

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/HU2004/000043

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-21
	No:	Claims	
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-21
Industrial applicability (IA)	Yes:	Claims	1-19,21
	No:	Claims	

2. Citations and explanations (Rule 70.7):

see separate sheet

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Reference is made to the following documents:

D1: T. Alexy et al., J. Cardiovasc. Pharmacol., March 2004, 43(3), p. 423-431 (P-document)
D2: WO01/21615
D3: WO00/32579
D4: Krishna M C et al., J. Med. Chem., 1998, 41(8), p. 3477-3492

Document D1 has been published between the priority date and the filing date of the present application. According to Rule 64.3 PCT, this document may not be taken into account for the assessment of novelty and inventive step during the international phase. The attention of the applicant is however drawn to the fact that this document may proved relevant in the examination process during regional phase.

The present application deals with 2-(N-containing heterocyclic) substituted benzimidazol-4-carboxamide derivatives as PARP inhibitors and antioxidants for the treatment of cancer, ischemia, inflammation, etc.

Re Item I
Basis of the report

The amendments filed with the telefaxes dated 28.02.2005 and 02.03.2005 introduce subject-matter which extends beyond the content of the application as filed, contrary to Article 34(2)(b) PCT.

No support could be found for the introductory part of claim 1 (also introduced on p. 1 of the description). Newly filed claims 3-10 are based on formulae (XI) to (XVIII), also disclosed in fig. 6/7 and 7/7. However, these formulae are nowhere disclosed in the application as filed and extend therefore beyond the content of the application as filed. The subject-matter of claims 12-21 is dependent on pending claim 1 which is not allowable under article 34(2)(b) PCT. Consequently, the subject-matter of these claims also extends beyond the content of the application as originally filed.

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claim 20 relates to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Document D2 describes 4-carboxamido-2-(N-containing)heterocyclylbenzimidazole derivatives as PARP inhibitors for use as antiinflammatory, immunosuppressive, etc. agents. According to table 1, compounds 28-30; table 3, compound 65; table 7, compounds 45-46 and table 13, compound 84, the G substituents present on ring A of D2 may represent a methyl group. The specific tetramethyl substitution pattern as claimed in the present application is not explicitly described in D2 and represents a new technical element. Novelty is acknowledged with regard to D2 (Art. 33(2) PCT).

   Document D3 discloses also 4-carboxamido-2-(N-containing)heterocyclyl benzimidazole derivatives as PARP inhibitors for the treatment of tumors, inflammation, etc. According to formula (Ia) of D3, the heterocyclic moiety A may only be substituted with 2 groups R^2 and R^3 (which may represent methyl) whereas the piperidine ring characteristic of the present claimed compound is at least tetrasubstituted. The subject-matter of claims 1 to 21 is also considered novel with regard to the disclosure of D3 (Art. 33(2) PCT).

   Document D4 reveals tetramethylpyrroline and tetramethylpiperidine derivatives as antioxidants. The compounds of D4 may be substituted by a bicyclic heteroring (see compounds 24c, 52b and tables 8-9). However, the use of a 4-carboxamidobenzimidazole substituent is not disclosed therein. Novelty is also acknowledged with regard to document D4 of the prior art (Art. 33(2) PCT).

2. Document D2, which is considered to represent the most relevant state of the art, describes 4-carboxamido-2-(N-containing)heterocyclyl benzimidazole derivatives as PARP inhibitors. The compounds of D2 differ from the present claimed subject-matter in the nature of the substituents present on the heterocyclic substituent.

The problem to be solved by the present invention may therefore be considered as the provision of further benzimidazole derivatives useful as PARP inhibitors for the treatment of inflammation, immunosuppressive disorders, etc.

The solution proposed in the present invention consists in the use of a tetramethyl substituted alicyclic nitrogenous ring. It is known from D2 that alicyclic nitrogenous ring (see for instance tables 8,10 and table 11, p. 41, compound 28) may be used in combination with a benzimidazole in the treatment of PARP-mediated diseases. According to claim 1 and formula (I) of D2, this alicyclic ring may be tetrasubstituted (1 to 4 G^1 groups). According to table 1, compounds 28-30; table 3, compound 65; table 7, compounds 45-46 and table 13, compound 84, the G substituents present on ring A of D2 may represent a methyl group. Furthermore, document D3 reveals the use of methyl substituents on a similar structure (see compound 266 and examples 8 and 19) for compounds exhibiting the same physiological activity. The skilled person would therefore regard it as an obvious alternative to include this feature in the compounds of D2 in order to solve the problem posed. Since methyl groups seem to be encompassed in the definition of G, the selection of such substituents on the cyclic amine would have been obvious to the skilled person. The fact that the nitrogen atom is sterically hindered cannot serve to establish the implication of an inventive step since such a possibility is also encompassed in D2 which suggests the use of up to 4 substituents. Therefore, the compounds of claim 1, the pharmaceutical compositions of claim 13, the processes of preparation of claims 16, 17 and 21 as well as the method of treatment of claim 20 do not seem to involve an inventive step in the sense of Art. 33(3) PCT in view of the teaching of D2 taken alone or in combination with D3.

Dependent claims 2-12, 14, 15, 18-19 do not seem to contain any features which, in combination with the features of any claim to which they refer, meet the requirements of the PCT in respect of inventive step (Art. 33(3) PCT).

3. For the assessment of the present claim 20 on the question whether it is industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for the manufacture of a medicament for a new medical treatment.

Re Item VIII
Certain observations on the international application

1. The compounds described in claim 11 on p. 30, l. 14-18 and l. 24-28 and on p. 8, l. 11-15 and 21-25 do not seem to fall within the scope of present claim 1. This inconsistency between the claims (and the description) leads to doubt concerning the matter for which protection is sought, thereby rendering the claims unclear (Art. 6 PCT).

2. The formulae (I^1), (I^1a), (I^1b), (I^1c) and (I^1d) of the invention referred to on page 11, l. 23 and in claim 16 have not been explicitly disclosed in the application and leaves the reader in doubt as to the meaning of the technical features to which it refers, thereby rendering the definition of the subject-matter of said claim unclear (Art. 6 PCT).

3. The compound disclosed in claim 11,p. 29, l. 33-34 and on p. 7, l. 30-31 of the description is unclear and leaves the reader in doubt as to the meaning of the technical features to which it refers, thereby rendering the definition of the subject-matter of said claim unclear (Art. 6 PCT).

2-TETRAMETHYL ALICYCLIC-AMINE- 4-CARBOXAMIDO-BENZIMIDAZOLES.

The invention relates to new biologically active chemical compounds, methods for their preparation, pharmaceutical compositions containing the same and methods for their use. More particularly the objects of the invention are 2-sterically hindered alicyclic-amine-substituted 4-carboxamido-benzimidazoles, their salts, their synthesis, their use as new antioxidants and PARP-inhibitors, as well as compositions comprising the new compounds for direct medical use and the use of the new compounds as intermediates for further useful chemicals and their preparation. The new compounds comprise two different bioactive functions - a sterically hindered pyrrolidine or piperidine and a 4-substituted-benzimidazole-carboxamid; as a consequence they show both PARP-inhibiting and antioxidant activities.

Abbreviations used in this specification:
PARP = poly(ADP-ribose)polymerase = poly-adenyl-ribosylase
NAD = nicotinamide adenine nucleotide
TBAR = thiobarbituric acid reacting substances
ROS = Reactive Oxidative Species,
RNS = Reactive Nitrogen Species
PARP-inhibitors = compounds inhibiting PARP.

The first objects of the invention are compounds containing a pyrrole, pyrrolidine or piperidine group the amino group of which is sterically hindered in both ortho positions by four methyl substitutions and their N-oxidized forms of the formula (I) and their pharmaceutically acceptable or technically applicable acid salts - where in the formula (I) the general formula (I) - where in the formula

R^1 represents hydrogen, $C_{(1-4)}$alkyl or $C_{(1-4)}$alkoxy
R^2 represents hydrogen, $C_{(1-4)}$alkyl, carboxyl, $C_{(1-4)}$ alkoxycarbonyl, carboxamido, aryl or hetero-aryl
R^3 represents hydrogen, $C_{(1-4)}$alkyl, aryl-methylene, or aryl
Y is a valency bond, a straight or branched chain $C_{(1-4)}$ alkene, a carbonyl-amino-$C_{(1-4)}$alkene, or a $-S-(CH_2)_m-$ group,
where all alkene groups above may be spaced by an arylene group,

AMENDED CLAIMS

1. Compounds containing a pyrrole, pyrrolidine or piperidine group the amino group of which is sterically hindered in both ortho positions by four methyl substitutions and their N-oxidized forms of the formula (I) and their pharmaceutically acceptable or technically applicable acid salts - where in the formula (I)

R^1 represents hydrogen, $C_{(1-4)}$ alkyl or $C_{(1-4)}$ alkoxy
R^2 represents hydrogen, $C_{(1-4)}$ alkyl, carboxyl, $C_{(1-4)}$ alkoxycarbonyl, carboxamido, aryl or hetero-aryl
R^3 represents hydrogen, $C_{(1-4)}$ alkyl, aryl-methylene, or aryl
Y is a valency bond, a straight or branched chain $C_{(1-4)}$ alkene, a carbonyl-amino- $C_{(1-4)}$ alkene, or a -S-$(CH_2)_m$- group,
where all alkene groups above may be spaced by an arylene group,
n represents zero or the integer 1
m represents the integer 1, 2 or 3
Q represents hydrogen, hydroxyl or the oxygen radical (O·) or together with the N atom of the adjacent ring forms a +N=O (oxoimmonium) group
Z represents a single or double bond
and their pharmaceutically acceptable or technically useful salts.

2. Compounds according to claim 1 where the substituents contain C_{1-4} alkyl as alkyl, C_{1-4} alkoxy as alkoxy, C_{1-4} alkoxycarbonyl as alkoxycarbonyl, phenyl as aryl, piperidine, pyrrole or pyrrolidine groups as heteroaryl groups, a C_{1-4} alkene as alkene, 6 or 12 membered arylene as arylene groups in any of the substituents where such groups are mentioned.

3. Compounds of general formula (XI) - where R^1 and R^3 represent the same as indicated in claim 1.

4. Compounds of general formula (XII) - where R^1 and R^3 represent the same as indicated in claim 1.

5. Compounds of general formula (XIII) - - where R^1 and R^3 represent the same as indicated in claim 1.

6. Compounds of general formula (XIV) - - where R^1 and R^3 represent the same as indicated in claim 1.

7. Compounds of general formula (XV) - where R^1 and R^3 represent the same as indicated in claim 1.

8. Compounds of general formula (XVI) - where R^1 and R^3 represent the same as indicated in claim 1.

9. Compounds of general formula (XVII) - where R^1 and R^3 represent the same as indicated in claim 1.

10. Compounds of general formula (XVIII) - where R^1 and R^3 represent the same as indicated in claim 1.

11. The following compounds in either of their forms according to claim 1 and their salts formed with pharmaceutically acceptable or technologically useful acids:

2-(1-oxyl-2,2,5,5-tetramethyl-2,5-dihydro-1*H*-pyrrol-3-yl)-1*H*-benzimidazole 4-carboxylic acid amide radical

2-(2,2,5,5-tetramethyl-2,5-dihydro-1*H*-pyrrol-3-yl)-1*H*-benzimidazole 4-carboxylic acid amide

4-(4-carbamoyl-1*H*-benzimidazol-2-yl)-1-oxyl-2,2,5,5-tetramethyl-pyrrolidine 3-carboxylic acid methyl ester radical

4-(4-carbamoyl-1*H*-benzimidazol-2-yl)- 2,2,5,5-tetramethyl-pyrrolidine-3-carboxylic acid methyl ester

2-(4-bromo-1-oxyl-2,2,5,5-tetramethyl-2,5-dihydro-1*H*-pyrrol-3-yl)-1*H*-benzimidazole 4-carboxylic acid amide radical

2-(4-bromo-2,2,5,5-tetramethyl-2,5-dihydro-1*H*-pyrrol-3-yl)-1H-benzimidazole 4-carboxylic acid amide

2-(1-oxyl-4-phenyl-2,2,5,5-tetramethyl-2,5-dihydro-1*H*-pyrrol-3-yl)-1*H*-benzimidazole 4-carboxylic acid amide radical

2-(4-phenyl-2,2,5,5-tetramethyl-2,5-dihydro-1*H*-pyrrol-3-yl)-1*H*-benzimidazole 4-carboxylic acid amide

2-[1-oxyl-2,2,5,5-tetramethyl-4-(3-trifluoromethyl-phenyl)-2,5-dihydro-1*H*-pyrrol-3-yl]-1*H*-benzimidazole 4-carboxylic acid amide radical

2-[2,2,5,5-tetramethyl-4-(3-trifluoromethyl-phenyl)-2,5-dihydro-1*H*-pyrrol-3-yl]-1*H*-benzimidazole 4-carboxylic acid amide

2-[4-(1-oxyl-2,2,5,5-tetramethyl-2,5-dihydro-1*H*-pyrrol-3-yl)-phenyl]-1*H*-benzimidazole 4-carboxylic acid amide radical

2-[4-(2,2,5,5-tetramethyl-2,5-dihydro-1*H*-pyrrol-3-yl)-phenyl]-1*H*-benzimidazole 4-carboxylic acid amide

2-(1,2,2,5,5-pentamethyl-2,5-dihydro-1*H*-pyrrol-3-yl)-1*H*-benzimidazole 4-carboxylic acid amide

2-(1-acetyl-2,2,5,5-tetramethyl-2,5-dihydro-1*H*-pyrrol-3-yl)-1*H*-benzimidazole 4-carboxylic acid amide

2-(1-methoxy-2,2,5,5-tetramethyl-2,5-dihydro-1*H*-pyrrol-3-yl)-1*H*-benzimidazole 4-carboxylic acid amide

2-[4-(dibenzofuran-4-yl)-1-oxyl-2,2,5,5-tetramethyl-2,5-dihydro-1*H*-pyrrol-3-yl)-phenyl]-1*H*-benzimidazole 4-carboxylic acid amide radical

2-[4-(dibenzofuran-4-yl)-2,2,5,5-tetramethyl-2,5-dihydro-1*H*-pyrrol-3-yl)-phenyl]-1*H*-benzimidazole 4-carboxylic acid amide

(1-hydroxy-2,2,6,6-tetramethyl-1,2,3,6-tetrahydro-pyridin-4-yl)-1*H*-benzimidazole 4-carboxylic acid amide

2-(2,2,6,6-tetramethyl-1,2,3,6-tetrahydro-pyridin-4-yl)-1*H*-benzimidazole 4-carboxylic acid amide

2-[4-(1-oxyl-2,2,5,5-tetramethyl-2,5-dihydro-1*H*-pyrrol-3-yl-methoxy)-phenyl]-1*H*-benzimidazole 4-carboxylic acid amide radical

2-[4-(2,2,5,5-tetramethyl-2,5-dihydro-1*H*-pyrrol-3-yl-methoxy)-phenyl]-1*H*-benzimidazole 4-carboxylic acid amide

2-[3-methoxy-4-(1-oxyl-2,2,5,5-tetramethyl-2,5-dihydro-1*H*-pyrrol-3-yl-methoxy)-phenyl]-1*H*-benzimidazole 4-carboxylic acid amide radical

2-[3-methoxy-4-(2,2,5,5-tetramethyl-2,5-dihydro-1*H*-pyrrol-3-yl-methoxy)-phenyl]-1*H*-benzimidazole 4-carboxylic acid amide

2-(5-oxyl-4,4,6,6-tetramethyl-4,6-dihydro-5*H*-thieno[2,3-c]pyrrol-2-yl)-1*H*-benzimidazole 4-carboxylic acid amide radical

2-(4,4,6,6-tetramethyl-4,6-dihydro-5*H*-thieno[2,3-c]pyrrol-2-yl)-1*H*-benzimidazole 4-carboxylic acid amide

2-(1-oxyl-2,2,5,5-tetramethyl-2,5-dihydro-1*H*-pyrrol-3-yl)-1*H*-benzimidazole 4-carboxylic acid isopropylamide radical

2-(2,2,5,5-tetramethyl-2,5-dihydro-1*H*-pyrrol-3-yl)-1*H*-benzimidazole 4-carboxylic acid isopropylamide

1-(2,2,5,5-tetramethyl-2,5-dihydro-1*H*-pyrrol-3-yl-methyl)-1*H*-benzimidazole 4-carboxylic acid amide radical;

1-(2,2,6,6-tetramethyl-1,2,3,6-tetrahydro-pyridin-4-yl)-1*H*-benzimidazole 4-carboxylic acid amide.

2-(1-oxyl-2,2,5,5-tetramethyl-2,5-dihydro-1H-pyrrol-3-yl-methylsulphanyl)-1H-benzimidazole 4-carboxylic acid amide radical

2-(2,2,5,5-tetramethyl-2,5-dihydro-1H-pyrrol-3-yl-methyl-sulphanyl)-1H-benzimidazole 4-carboxylic acid amide

2-(1-oxyl-2,2,6,6-tetramethyl-1,2,3,6-tetrahydro-pirydin-4-yl-methylsulphanyl)-1H-benzimidazole 4-carboxylic acid amide

2-(2,2,6,6-tetramethyl-1,2,3,6-tetrahydro-pyridin-4-yl-methylsulphanyl)-1H-benzimidazole 4-carboxylic acid amide and its hydrochloric acid salt.

12. Compounds according to any of claims 1 to 11 in the form of their salts formed with inorganic or organic acids said salts being technologically useful such as oxalates or pharmacologically acceptable such as hydrochlorides, hydrobromides, sulphates, phosphates, phosphites, borates, lactates, ascorbates, acetates, fumarates, formiates, tosylates, tartarates, maleates, citrates, gluconates, besylates etc.

13. Pharmaceutical compositions comprising as active ingredients in an effective dose of compounds according to any of the claims 1 to 11 or their pharmaceutically acceptable salts for the treatment of diseases which can be favourably influenced by scavanging oxidative stress and/or PARP inhibition.

14. Pharmaceutical compositions according to claim 13 comprising as active ingredients in an effective dose compounds according to any of the claims 1 to 10 or their pharmaceutically acceptable salts for treatment of ischemia/reperfusion, inflammations and/or potentiation of cancer therapies.

15. Pharmaceutical compositions according to claim 13 or 14 which appear in formulations for oral, transdermal, parentheral, intramuscular, intravenous administration e.g. in the following forms: tablets, injections, solutions, suppositories, patches, suspensions etc.

16. Process for the preparation of compounds of the general formula (I^1) and their pharmaceutically acceptable or technically applicable acid salts - where in the formula R^1 represents hydrogen, $C_{(1-4)}$ alkyl or $C_{(1-4)}$ alkoxy

R^2 represents hydrogen, $C_{(1-4)}$ alkyl, carboxyl, $C_{(1-4)}$ alkoxycarbonyl, carboxamido, aryl or hetero-aryl

R^3 represents hydrogen, $C_{(1-4)}$ alkyl, aryl-methylene, or aryl

Y^1 is a valency bond, a straight or branched $C_{(1-4)}$ alkene, a carbonyl-amino- $C_{(1-4)}$ alkene,

where all alkene groups above may be spaced by an arylene group,

n represents zero or the integer 1

m represents the integer 1, 2 or 3

Q represents hydrogen, hydroxyl or the oxygen radical (O·) or together with the N atom of the adjacent ring forms a +N=O (oxoimmonium) group

Z represents a single or double bond

comprising reacting a carboxamide of the general formula (IV) - where

R^1 has the meaning as stated above -

with a heterocyclic derivative of the general formula (V) or (VI) - where

R^2, Y, Z and n have the meaning as stated above.

17. Process for the preparation of compounds of the general formula (IX) - where in the formula

R^1 represents hydrogen, $C_{(1-4)}$ alkyl or $C_{(1-4)}$ alkoxy

R^2 represents hydrogen, $C_{(1-4)}$ alkyl, carboxyl, $C_{(1-4)}$ alkoxycarbonyl, carboxamido, aryl or hetero-aryl

R^3 represents hydrogen, $C_{(1-4)}$ alkyl, aryl-methylene, or aryl

where all alkene groups above may be spaced by an arylene group,

n represents zero or the integer 1

m represents the integer 1, 2 or 3

Q represents hydrogen, hydroxyl or the oxygen radical (O·) or together with the N atom of the adjacent ring forms a +N=O (oxoimmonium) group

Z represents a single or double bond

and their pharmaceutically acceptable or technically useful salts *comprising*

reacting a compound of the general formula VII - where R^1 has the meaning as above -

with an alkylating agent of general formula VIII - where R^2, Z, Q, n and m have the meaning as stated above and X stands for a leaving group capable to react with the mercapto group to form a thioether

and optionally changing the substituents Q by way of oxydation and/or reduction to obtain the desired change in the substituents Q.

18. Process according to claim 17 where as a compound of formula VIII a correspondingly substituted alkyl-halogenide or alkyl-sulphonate is used such as any member of the group selected of the type alkyl chloride, alkyl bromide, alkyl-iodide, alkyl-mesylate, alkyl-tosylate, alkyl-triflate and the reaction is carried out in the presence of a base.

19. Process according to any of claims 17 to 18 *comprising* preparing any of the compounds of claim 1 to 11 in the form of its technologically useful salts such as oxalates or pharmacologically acceptable salts such as hydrochlorides, hydrobromides, sulphates, phosphates, phosphites, borates, lactates, ascorbates, acetates, fumarates, formiates, tosylates, tartarates, maleates, citrates, gluconates, besylates.

20. Method of treatment of diseases which are based on PARP activation or are caused by Reactive Oxidative Species (ROS) and Reactive Nitrogen Species (RNS) specifically cases of ischemia/reperfusion, inflammation, unfavourable reaction on the course of radiotherapy or chemotherapy by administration to the patient in need of such treatment an effective dose of at least one compound of the general formula I or its pharmaceutically acceptable salt - where in the formula

R^1 represents hydrogen, $C_{(1-4)}$alkyl or $C_{(1-4)}$alkoxy

R^2 represents hydrogen, $C_{(1-4)}$ alkyl, carboxyl, $C_{(1-4)}$ alkoxy-carbonyl, carboxamido, aryl or hetero-aryl

R^3 represents hydrogen, $C_{(1-4)}$alkyl, aryl-methylene, or aryl

Y is a valency bond, a straight or branched chain $C_{(1-4)}$ alkene, a carbonyl-amino-$C_{(1-4)}$alkene, or a -S-$(CH_2)_m$-group,

where all alkene groups above may be spaced by an arylene group,

n represents zero or the integer 1

m represents the integer 1, 2 or 3

Q represents hydrogen, hydroxyl or the oxygen radical (O·) or together with the N atom of the adjacent ring forms a +N=O (oxoimmonium) group

Z represents a single or double bond

in the form of a dosage form comprising said effective dose.

20. Process for the preparation of pharmaceutical formulations which can be used for the treatment of diseases which are caused by Reactive Oxidative Species (ROS) and Reactive Nitrogen Species (RNS) or are based on

PARP activation such as ischemia/reperfusion, inflammation, unfavourable reaction on the course of radiotherapy or chemotherapy by formulation of compounds of the general formula (I) or its salts - where in the formula

R^1 represents hydrogen, $C_{(1-4)}$alkyl or $C_{(1-4)}$alkoxy

R^2 represents hydrogen, $C_{(1-4)}$alkyl, carboxyl, $C_{(1-4)}$ alkoxy-carbonyl, carboxamido, aryl or hetero-aryl

R^3 represents hydrogen, $C_{(1-4)}$alkyl, aryl-methylene, or aryl

Y is a valency bond, a straight or branched chain $C_{(1-4)}$alkene, a carbonyl-amino-$C_{(1-4)}$ alkene, or a $-S-(CH_2)_m-$ group,

where all alkene groups above may be spaced by an arylene group,

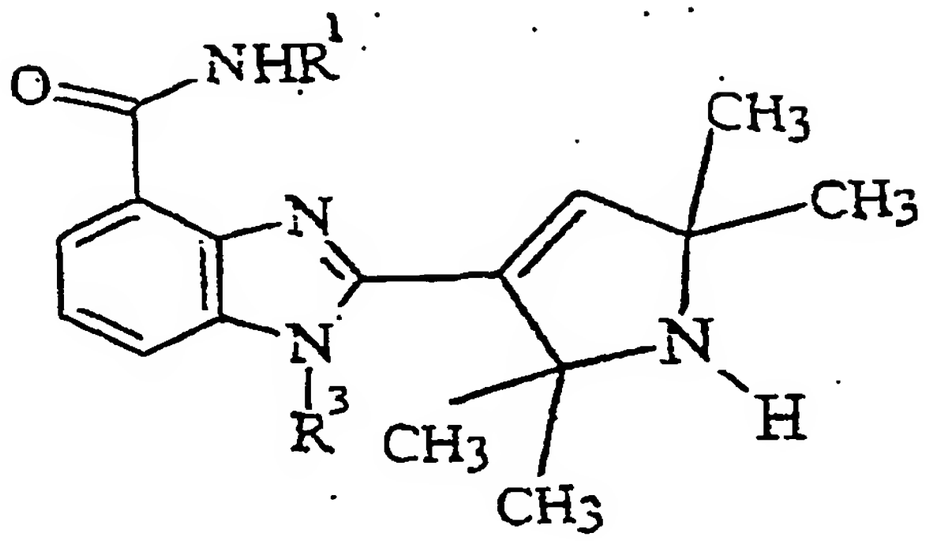
n represents zero or the integer 1

m represents the integer 1, 2 or 3

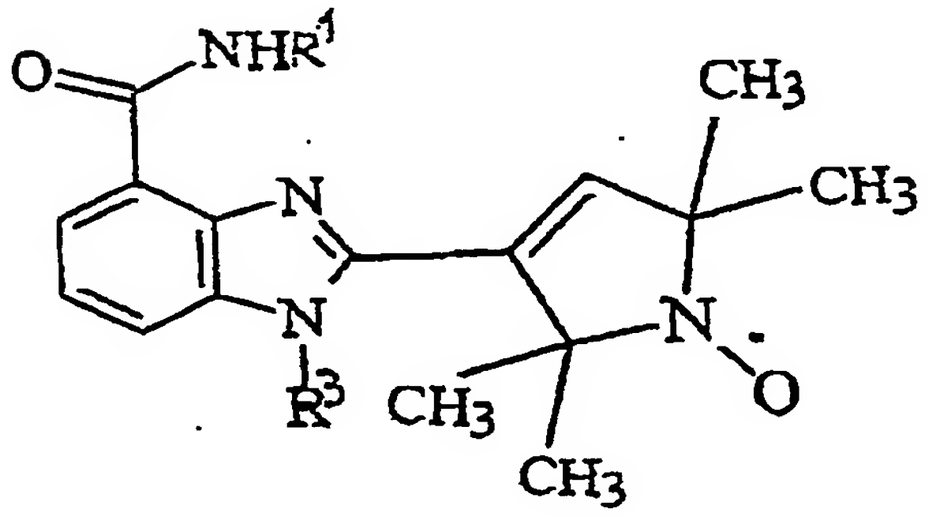
Q represents hydrogen, hydroxyl or the oxygen radical (O·) or together with the N atom of the adjacent ring forms a +N=O (oxoimmonium) group

Z represents a single or double bond

with usual additives into ready to use dosage forms by methods known per se.



XI



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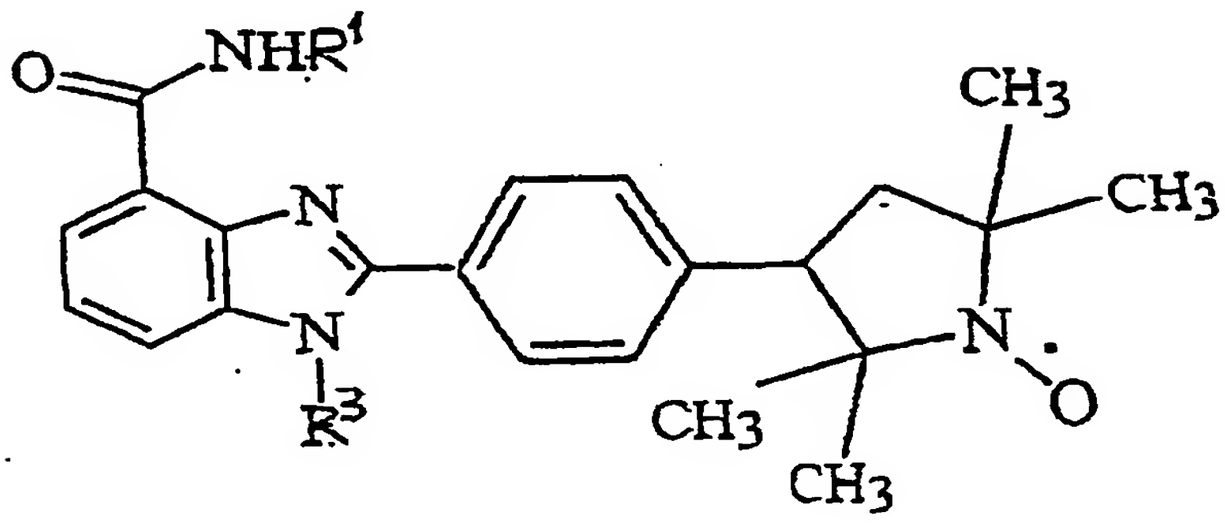

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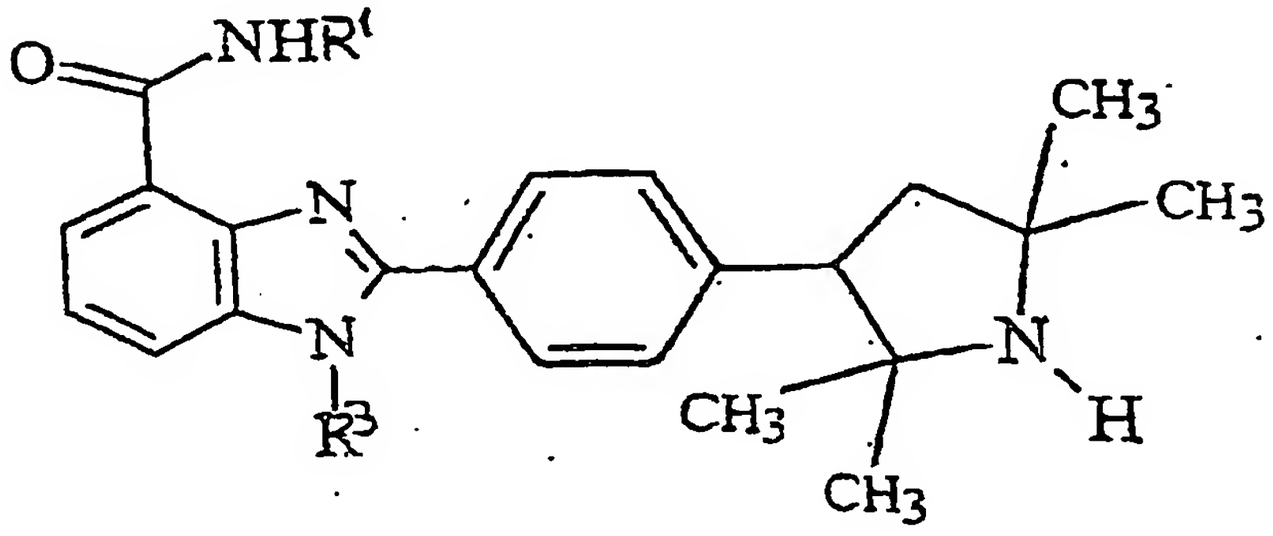
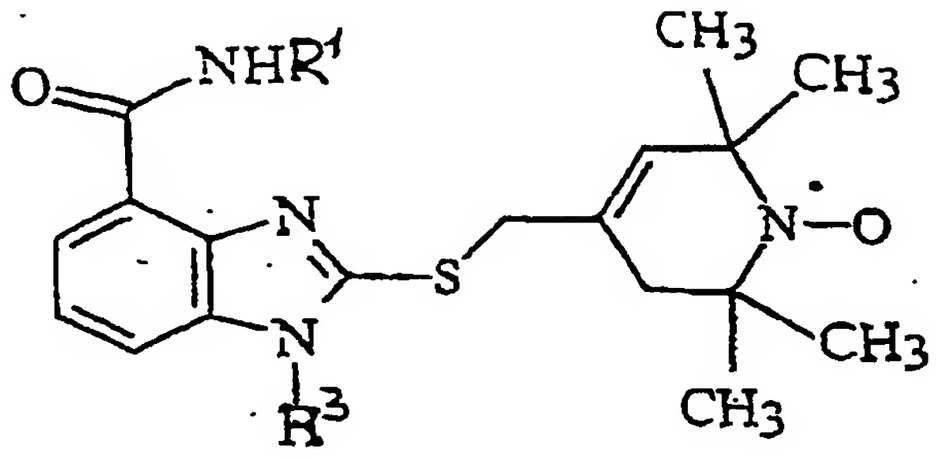
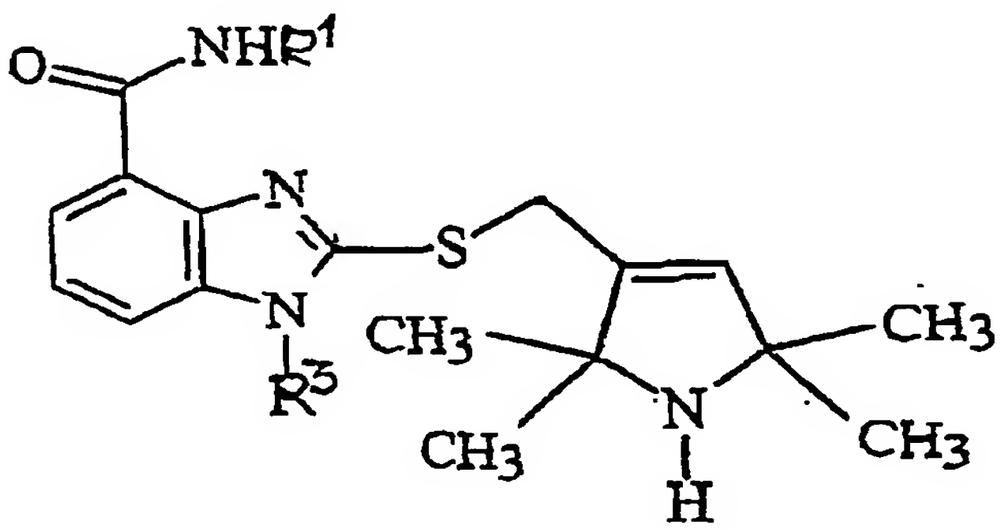


XIV

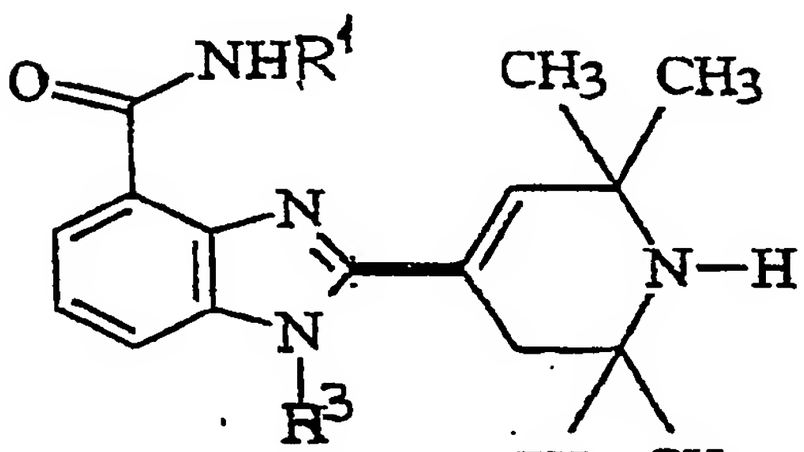
FIGURE 6



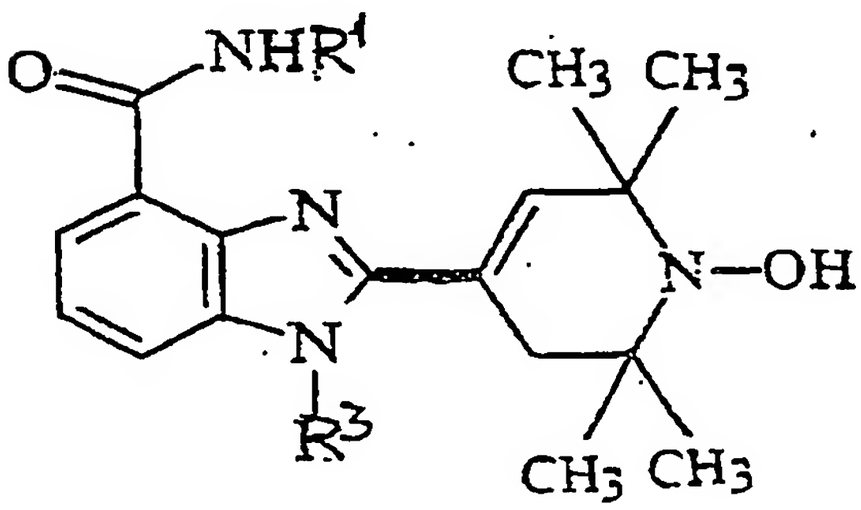
XV



XVI



XVII



XVIII

FIGURE 7